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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 24

Application Number: 09/206,040
Filing Date: December 4, 1998
Appellant(s): Joseph R. Byrum, Thomas J. La Rosa, and Gregory R. Heck

David R. Marsh and June E. Cohan
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed January 31, 2001.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the brief does not contain arguments that claims 1-3 do not stand or fall together with respect to the rejections under 35 USC 101 and 35 USC 112, first paragraph due to a lack of specific and substantial utility. With respect to the additional rejection of

claims 1 and 3 under 35 USC 112, first paragraph for lack of an enabling disclosure and the rejection of claims 1 and 3 under 35 USC 112, first paragraph for lack of an adequate written description, the brief does not argue the separate patentability of claim 1 from claim 3 with respect to these rejections.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

Taxonomy Browser on the World Wide Web at ncbi.nlm.nih.gov/htbin-post/Taxonomy.

Ahmad et al. (1979) J. Hered. 70: 358-364.

The following art cited during prosecution (Paper No. 14) in response to arguments previously made by Appellants, but not reiterated in the Brief, indicate the state of the art:

Hayashi, "Manipulation of DNA by PCR", in The Polymerase Chain Reaction, Mullis et al. (eds.), Birkhauser: Boston, pp. 3-13, 1994.

Kitchin et al., Nature 344: 201, 1990.

Roux, PCR Meth. Appl. 4 (5): S185-S194, 1994.

Shuldiner et al., Nucleic Acids Res. 17 (11): 4409, 1989.

Kurata et al., Nature Genetics 8: 365-372, 1994.

Shi et al., J. Hered. 87: 308-313, 1996.

Cha et al., "Specificity, efficiency, and fidelity of PCR", in PCR Primer: A Laboratory Manual, Dieffenbach et al. (eds.), Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, pp. 37-51, 1995.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 101

Claims 1-3 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The invention is drawn to nucleic acid molecules either consisting of, consisting essentially of, or comprising the nucleotide sequence as set forth in SEQ ID NO: 1. The nucleic acid molecule set forth as SEQ ID NO: 1 is an expressed sequence tag, or EST, made as a partial cDNA from an mRNA isolated from a young seed pod (5 to 15 days post-flowering) from *Glycine max* (soybean) cultivar Asgrow 3244. In the art, an EST is a tag or molecular marker for a corresponding mRNA that contains it and for the corresponding gene which expresses that mRNA. The utilities disclosed for the EST of SEQ ID NO: 1 or fragment thereof, or a nucleic acid molecule comprising same are:

- Use the EST as a probe for screening to identify sequence polymorphisms linked to the sequences corresponding to the claimed nucleic acid molecule in a genome, and then use as a probe for detecting the polymorphisms, which serve as a molecular marker,

either a) for a mutation affecting the expression of a product encoded, at least in part, by the claimed nucleic acid molecule (specification, pages 27-28) or b) for a desirable trait that is genetically linked to the polymorphism (specification, pages 35-36);

-Use of the EST as a probe for detecting a physical map location, e.g. as a marker in *in situ* hybridization;

-Use as a probe or source of PCR primers either to isolate other nucleic acid molecules (e.g. complete cDNA, protein coding sequence, genomic fragment, promoter, start of a chromosome walk) from the same organism or different organisms, i.e. other plants, or to detect other nucleic acid molecules (e.g. mRNA, chromosomal region, chromosome). Disclosed for the latter, for example, is to detect the mRNA in different tissues or as a measure of protein expression from the mRNA (based on mRNA levels), particularly if there is a mutation (hypothetical) affecting expression;

-Use of the EST as an antisense inhibitor of the corresponding mRNA; and

-Use as a probe to identify or isolate proteins that might bind to the EST sequence.

Each of these utilities requires additional knowledge about the EST before the EST can be used for a specific purpose, such as: whether there are sequence polymorphisms linked to the gene corresponding to the EST and, if so, their identity; the map location of the corresponding gene; the sequence of the corresponding complete mRNA sequence, protein coding sequence or genomic sequence; the function of the protein encoded by the corresponding mRNA; the identity and phenotype, if any, of a mutation in the corresponding

gene; the tissue distribution of the corresponding mRNA and tissue-specific expression levels; *etc*. The specification does not provide any such information specific to the disclosed EST. Consequently, the disclosed utilities are *non-specific* utilities, since any of the general disclosed utilities would apply equally to any uncharacterized nucleic acid molecule from soybean in particular, or plants in general. Moreover, since practice of these utilities would first require research on the disclosed EST itself, i.e. there is no apparent *immediate* benefit to the public. The only readily apparent *immediate* use for the disclosed EST is as an object of further scientific inquiry aimed at characterization of the EST itself in terms of identity of corresponding sequence polymorphisms (if any), map location, sequence and function of the corresponding mRNA and polypeptide, tissue distribution of the corresponding mRNA and polypeptide, *etc*. These *immediate* uses are merely searches for a specific and substantial statutory utility for the claimed invention that fail to meet the statutory utility requirement. In *Brenner v. Manson*, 148 USPQ 689, 696 (US, 1966), the Court held that "Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing", and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." The original disclosure lacks any successful conclusion for even one of the vague and general utilities disclosed. Thus, no "substantial" or "real world" utility has been disclosed.

Further, there is no evidence of a well-established utility for the disclosed EST or claimed nucleic acid molecules.

Claim Rejections - 35 USC § 112 (Enablement)

Claims 1-3 stand also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition, claims 1 and 3 contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention as directed to nucleic acid molecules comprising or consisting essentially of the EST of SEQ ID NO: 1 and additional nucleotide sequences linked to the EST.

The recitation of "consisting essentially of" in claim 3 has been treated as being equivalent to "comprising", as recited in claim 1. There is nothing on the record to indicate how "consisting essentially of" alters the scope of claim 3 compared to claim 1. Thus, claim 3 would not exclude any embodiment embraced by claim 1.

The claims are not enabled because the specification fails to teach one of skill in the art how to use the claimed nucleic acid molecules, such that one of skill in the are could identify a target nucleic acid without undue experimentation. All of the utilities disclosed for the claimed nucleic acid molecules require hybridization to some target nucleic acid, in some

capacity. Claims 1 and 3 embrace an essentially infinite genus of nucleic acid molecules comprising or consisting essentially of SEQ ID NO: 1 even when just considering nucleic acid sequences and ignoring nucleic acid molecules comprising non-nucleotide moieties. The specification does not explicitly disclose any nucleic acid molecules that "comprise" SEQ ID NO: 1, other than SEQ ID NO: 1 itself, either unlabeled or labeled with a detectable non-nucleotide moiety such as a fluorophor, and a deposited clone from which SEQ ID NO: 1 was identified. No other specific nucleic acid molecules are disclosed wherein the nucleic acid sequence is extended beyond contiguous nucleotides present in SEQ ID NO: 1.

The specification does not teach the maximum length or location (5' end, 3' end, or both ends) of nucleic acid sequence(s) that could be added to SEQ ID NO: 1, that would not interfere with its disclosed use as a hybridization probe. The specification provides no guidance whatsoever other than labeling a nucleic acid molecule "consisting of" SEQ ID NO: 1 or an oligonucleotide fragment of SEQ ID NO: 1. The only working example demonstrates using a claimed nucleic acid molecule, the deposited clone, as a template for PCR sequencing, i.e. experimentation on the claimed invention.

Without knowing the composition of the target DNA, such as the size of a corresponding mRNA, the size of a specific genomic DNA, restriction endonuclease fragment or amplified fragment, or the extraneous sequences that may be added to the probe or primer, one would be unable to predict whether the probe or primer would function as expected under any given reaction conditions to hybridize or amplify a specific nucleic acid molecule

corresponding to the intended target. Since the claims embrace adding any and all nucleic acid sequences to the core nucleic acid molecule of SEQ ID NO: 1, one cannot predict whether or not the additional nucleic acid sequence added would hybridize to a target nucleic acid molecule other than the intended target nucleic acid molecule. When such a situation occurs, and more than one nucleic acid molecule is amplified or detected in hybridization, the skilled artisan would have no information that would allow the desired target nucleic acid molecule to be distinguished from a nucleic acid molecule that was targeted by the added nucleic acid sequences. This simple situation would be further complicated if SEQ ID NO: 1 or the intended target nucleic acid were one of a number of different repeated nucleotide sequences in a sample or if the added nucleotide sequence comprised one of a number of different repeated nucleic acid sequences in a sample, each with varying degrees of binding specificity under hybridization or amplification reaction conditions between primer or probe and target nucleic acid molecules. One cannot predict whether either the intended target nucleic acid or nucleic acid sequences added to a probe or primer are one of a number of repeated nucleic acid sequences; trial and error experimentation would be required.

Consequently, making the myriad of nucleic acid molecules embraced by the claims and testing the suitability of each for use as a probe or primer for the disclosed utilities in the absence of guidance or examples would require excessive trial and error experimentation due to the unpredictability involved, and would therefore require undue experimentation.

Claim Rejections - 35 USC § 112 (Written Description)

Claims 1 and 3 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 3 are drawn to nucleic acid molecules "comprising" or "consisting essentially of" the EST of SEQ ID NO: 1; and therefore to an astronomically large genus of nucleic acid molecules comprising SEQ ID NO: 1 even solely considering nucleic acid sequences and ignoring nucleic acid molecules comprising non-nucleotide moieties such as detectable labels. The specification does not explicitly disclose any nucleic acid molecules that "comprise" or "consist essentially of" SEQ ID NO: 1, other than that of SEQ ID NO: 1 itself (either unlabeled or labeled with a detectable non-nucleotide moiety such as a fluorophor) and the clone from which the sequence was derived. Any additional cDNA sequence that may be present on the clone was not described other than by deposit. No nucleic acid molecules are disclosed wherein the nucleic acid sequence is extended beyond SEQ ID NO: 1, other than solely by implication a larger EST or mRNA comprising SEQ ID NO: 1. However, the specification does not disclose the structure of any such larger nucleic acid molecule or EST or mRNA. The disclosure of the single nucleic acid molecule set forth as SEQ ID NO: 1 does not adequately describe the astronomically large number of possible nucleic acid molecules embraced by claims 1 and 3.

(11) Response to Argument

Overview

The brief focuses primarily on two utilities mentioned above - the claimed nucleic acid molecules can be used as a hybridization probe; a) "to identify the presence or absence of a polymorphism" and b) "for expression profiling" of the mRNA corresponding to the claimed nucleic acid molecules. Additional disclosed general utilities discussed in the brief are as sense and antisense inhibitors of the gene corresponding to the claimed nucleic acid molecules, and as hybridization probes to identify corresponding nucleic acid molecules from other plant species, or to identify clones containing soybean genomic DNA physically linked to the genomic DNA corresponding to the claimed nucleic acid molecule, e.g. as an initial step in a chromosome walk. With respect to some of the general utilities mentioned in the rejection, the brief (at page 9, 2nd full para.) states:

> It is irrelevant whether the corresponding mRNA or polypeptide themselves have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed nucleic acid molecules.

This statement in the brief concerning the utility of the corresponding mRNA or polypeptide, are consistent with the Examiner's position that the specification does not disclose a specific, substantial and credible utility for either the corresponding mRNA or protein, and therefore for the claimed nucleic acid molecules in the context of being useful in a process to isolate the corresponding mRNA and protein.

Response to Appellants' Specific Arguments

Appellant's arguments are addressed *seriatum*. References in the brief to page numbers in the Advisory action are incorrect. Appellants' representative informed the Examiner that a courtesy copy of this action, which had been FAXed to them, had been inadvertently used to prepare the brief. The subject matter may be found in the Advisory action on file one (sometimes two) page(s) prior to that cited in the brief. Where the Advisory action is discussed below, the correct page numbers are referred to.

A) Response to Brief Section 8.A.

Appellants assert that the claimed invention meets the utility and enablement requirements because they have proven that the claimed nucleic acid molecules can be used "to identify the presence or absence of a polymorphism" and "as a hybridization probe for expression profiling". Appellants also assert that the specification has provided an adequate description for nucleic acid molecules "comprising" or "consisting essentially of" the sequence of SEQ ID NO: 1, because the only structural feature necessary for the operability of the claimed invention is the presence of the common structural feature, i.e. the nucleotide sequence of SEQ ID NO: 1.

The brief (footnotes 1 and 4) states that the Examiner (Advisory Action of 11/22/00, page 13 [*sic*: 12]) conceded that the use "to identify the presence or absence of a polymorphism" had been proven. However, the only concession made by the Examiner on page 12 of the Advisory Action was that the Wiegand Declaration showed that a

"polymorphism" could be detected between two species of plant. This information and utility was absent from the original disclosure (discussed in more detail below).

B) Response to Brief Section 8.B.

Appellant argues that the analysis of the Wiegand Declaration was in error and legally wrong and that the reliance upon *In re Kirk*, 153 USPQ 48 (CCPA 1967) was misplaced. The argument suggests that the Examiner did not consider the Wiegand Declaration. Appellants take exception to the excerpt from page 2 of the Advisory Action where the Examiner stated: "Since this new information was not disclosed in the original specification, it *could not be* included in any evaluation of utility for the claimed invention" (emphasis added). The new information described in the Wiegand Declaration *could not be* evaluated prior to the Advisory Action because the information had not been provided previously - such as within the four corners of the original specification. The subsequent 19 pages of the Advisory Action clearly show that the Examiner did consider the evidence presented in the declaration. The Examiner concluded that the evidence did not show that the utility and enablement requirements had been met at the time the application was filed, based upon the specification originally filed. It is noted that Appellants agree with the Examiner that the *disclosure* must meet the utility and enablement requirements at the time the application was filed (brief, page 5).

Like the Petrow Declaration in *Kirk*, the Wiegand Declaration provided evidence supporting a holding of a lack of specific and substantial utility. That is, the Declaration shows that further experimentation would have been necessary at the time the application was

filed in order to begin the process of finding a specific and substantial utility for the claimed invention that corresponded to one of the vague and general assertions of utility presented in the specification. The court in *Kirk* (pages 52-53) agreed with the Appellants that the Petrow declaration disclosed specific biological properties possessed by the claimed invention that were consistent with the vague and general biological properties disclosed, i.e. some properties possessed by some prior art steroids. However, the court held that the declaration did not help appellants cause, because it amounted to "an admission that experimentation would be necessary to determine actual uses-or possible lack of uses-of the compounds, as well as how to employ them in a useful manner". The court held that whether the claimed compounds "do *in fact* possess specific ... activity or usefulness" was not at issue, but rather "what the compounds are *disclosed* to do that is determinative".

Appellants suggest that the instant situation is more analogous to *In re Brana*, 34 USPQ2d 1436, 1440 (CA FC 1995) than to *Kirk*. However, the situation in *Brana* can be distinguished. *Brana*, which addresses the sufficiency of evidence supporting a disclosed specific utility, is inappropriate because appellants have not disclosed any specific utility for the claimed SEQ ID No. 1. In fact, *Brana* reaffirms the decision in *Kirk* because the court emphasized that if the specification had failed to disclose the specific utility which was substantiated by the declaration, the invention would have lacked utility. The instant specification is analogous to the situation in *Kirk* because it fails to disclose *a single* specific

and substantial utility that would involve using the claimed invention as a hybridization probe or in any other capacity.

The Wiegand Declaration does not substantiate or confirm any specific and substantial utility *disclosed in the specification*. Rather, it attempts to add missing, specific disclosure to the application. For example, the specification does not suggest that one should identify sequence differences between two different species of *Glycine, Glycine max* and *Glycine soja*, as described in paragraphs 20-23 of the Wiegand Declaration, much less suggest a reason for doing so. Also, the specification does not disclose that the corresponding mRNA is present in young soybean sprouts and adult soybean leaves, nor does it suggest any significance to such expression in these samples (or in young soybean seed pods, as disclosed) in the context of a specific utility.

C) Response to Brief Section 8.C.

The Examiner's position on footnote 4 (brief, page 8), is set out in section A, *supra*.

D) Response to Brief Section 8.C.(1).

Appellants indicate that the Final action was unclear in stating "Generalized utilities lack the specific correspondence between the asserted utility and the claimed subject matter required by the statute" (page 8 of final Office action). In response, the specification describes, in general, a variety of uses for nucleic acid molecules, like ESTs, that had been practiced in the art, such as the detection of a polymorphism. However, each specific nucleic acid molecule has specific uses that are very different from those for a different specific

nucleic acid molecule. For example, an allele specific probe for determining the specific haplotype of a human HLA DR antigen cannot be used as a probe for detecting a specific polymorphism associated with the Bloom's disease locus or the cystic fibrosis disease locus. The specification generally teaches using the claimed polynucleotides to identify a polymorphism, but fails to teach that a polymorphism could in fact be detected, or a specific polymorphism that could be detected. The specification generally teaches using a polymorphism, detectable with the claimed nucleic acid molecules, as a molecular marker for a linked trait of interest, but fails to teach either the polymorphism or the trait of interest. The court in *Kirk* (at page 53) held:

> We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.

Similarly, the specification generally teaches using the claimed polynucleotide to measure the amount of mRNA in a tissue sample, such as in tissue profiling. However, except for the inference that the corresponding mRNA is present in at least one tissue of young soybean seed pods, the specification does not disclose any information on what other tissues express the corresponding mRNA, what level of expression occurs in these tissues, or whether the expression levels are regulated developmentally or in response to environmental conditions, or any scientific or practical significance for the expression. Significantly, the specification

fails to teach any specific practical use for such information as it relates specifically to the claimed invention.

The Examiner concedes the specification did disclose at least one other "fact" concerning the claimed nucleic acid molecules in addition to SEQ ID NO: 1 - young seed pods express the corresponding mRNA. However, the Examiner stands by the "fact" that the specification fails to disclose any specific correspondence between these characteristics and any specific and substantial use for the claimed nucleic acid molecule. For example, the specification fails to identify even a single polymorphism *known*, by Appellant at the time the application was filed, to be detectable by the claimed nucleic acid molecules.

Appellant appears to concede that the specification does not disclose any specific and substantial utilities that would require the complete structure of the corresponding mRNA and protein. As the brief (at page 9, 2nd full para.) states:

> It is irrelevant whether the corresponding mRNA or polypeptide themselves have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed nucleic acid molecules.

The Wiegand Declaration does indeed show (para. 22-23) that the claimed nucleic acid molecule can be used to detect a sequence difference between *Glycine max* and *Glycine soja*. Appellants assert that because "the claimed nucleic acid molecules work for the disclosed utilities, there is clearly a connection (correspondence) between the disclosed utilities and the claimed invention". However, the specification does not disclose such a use - in fact the specification does not mention *Glycine soja* at all. Therefore, all the Wiegand Declaration

shows is a correspondence between the claimed invention and a specific utility disclosed in the Wiegand Declaration. In *Kirk*, the Petrow declaration had shown that some of the claimed compounds actually had a specific biological activity, however, this finding was not deemed dispositive by the Court because it is "what the compounds are *disclosed* to do that is determinative".

The brief states (page 10) that the specification teaches introducing the claimed nucleic acid molecules into a plant or plant cell as an antisense or sense inhibitor, and then using the plant or plant cell for screening compounds as herbicides. However, the specification does not disclose such a utility. The specification (page 64, line 19 to page 64, line 22) teaches that the claimed invention can be used to encode a sense or antisense inhibitor. However, the specification does not show that the claimed invention can be used either as a sense or antisense inhibitor or in screening compounds as herbicides. Additionally, the specification does not teach any consequence that would result from such inhibition, or how such inhibition would be useful in a "real world" context. Therefore, claimed invention has no *immediate* use in this context other than as an object of further scientific investigation in order to first confirm whether the claimed nucleic acid molecule can in fact be used as a sense or antisense inhibitor, and, if it can, to then determine a "real world" use for such inhibition. Thus, the specification provides no specific and substantial utility for the claimed invention as a sense or antisense inhibitor. This utility is neither specific nor substantial because the specification does not disclose: 1) that it had been carried out; 2) what inhibition to measure or how to measure it; 3)

what result would have been obtained if it had been carried out; or 4) what practical benefit would have arisen by using the claimed invention in this manner. For all of these reasons, Appellants' arguments equating this speculative screen to some nebulous "cell-based assay" are therefore unpersuasive.

The brief asserts that using the claimed nucleic acid molecule for "expression profiling" meets the statutory utility requirement. The specification does not discuss "expression profiling" *per se*. It does teach (pages 12, line 20 to page 13, line 16; page 36, line 19 to page 40, line 6) using the claimed nucleic acid molecules to determine whether an mRNA, and by inference a protein, that corresponds to the claimed nucleic acid molecule is present in a particular cell or tissue. Since the nucleic acid of SEQ ID NO: 1 was obtained from young soybean seed pods, it can be inferred that at least one tissue present in young seed pods expresses an mRNA corresponding to the claimed nucleic acid molecule. The specification generally describes various methods known in the art for detecting mRNA in biological samples.

However, the specification fails to disclose any practical reason for doing so, or any *immediate* benefit that the public may derive from doing so. The specification does not disclose which of the different tissues or cells present in the young seed pods express the corresponding mRNA. The specification does not disclose what other cells and tissues of a soybean plant express or do not express the corresponding mRNA. The specification discloses no environmental conditions which would increase or decrease expression of the corresponding

mRNA. Nor does the specification disclose any phenotype or trait that would be conferred on a plant, tissue, or cell as a result of overexpression or underexpression of the corresponding gene relative to wild-type expression levels, or as a result of expression of the corresponding gene at inappropriate times during plant development or in inappropriate tissues or cells in a plant. While the claimed invention could clearly be used to provide such information, until such information is known, one skilled in the art can only guess at the result and can only guess at what practical benefit or specific and substantial utility may arise from such information. Therefore, the only readily apparent utility for obtaining such information is to aid in elucidating the biological function of the corresponding gene and its expression products. As such, this disclosed utility is directed at using the claimed invention in order to characterize itself, perhaps with the hope that the information may suggest a practical utility to one skilled in the art. Thus, this argument is not persuasive.

The Wiegand Declaration shows that the claimed nucleic acid molecule can be used to detect a specific mRNA or for measuring the amount of mRNA in a sample, but the specification fails to disclose any practical benefit, i.e. a substantial utility, for doing so. Any *bona fide* EST can be used to detect the mRNA from which it was made and measure the amount of such mRNA in various samples, such as tissue. However, unless some biological or physiological significance can be attached to the expression pattern or level, it is unclear what practical benefit would be obtained, in the absence of any further information. The specification fails to disclose any "real world" significance either to the expression pattern or

the expression level of the corresponding mRNA in any plant cell or tissue. The specification does not disclose what tissues normally express the corresponding mRNA (other than young seed pods) or at what levels (in any tissue, including young seed pods); nor does it disclose what environmental stimuli affect the levels of mRNA expression or how the expression levels change in response to any one stimulus. For example, if young seed pods of a particular soybean variety were found to contain elevated levels of the corresponding mRNA when grown in the field as compared to being grown in a greenhouse, would that mean that the field-grown plant was suffering - or benefitting - from the field growth conditions. If the field-grown plants were suffering, would it be from drought-stress, over watering, too much light, too little light, or something else? Appellants argue in footnote 8 of the brief (page 11) that using the claimed nucleic acid molecules to characterize the expression of the corresponding mRNA is not research on the claimed invention itself. The Examiner disagrees.

First, since the SEQ ID NO: 1 is a partial sequence, i.e. an EST, of a cDNA that is presumed to be a faithful copy of part of an mRNA existing in young seed pods, SEQ ID NO: 1 is then presumed to be a partial sequence of that corresponding mRNA. Consequently, that corresponding mRNA *is* a nucleic acid molecule comprising or consisting essentially of the nucleotide sequence of SEQ ID NO: 1 or its complement, and the part of the mRNA that is identical to SEQ ID NO: 1 *is* a nucleic acid molecule consisting of SEQ ID NO: 1 or its complement. Therefore, the use of the claimed nucleic acid molecules in assays to determine which plant tissues contain the corresponding mRNA and in what amounts, or in assays to

determine the levels of the corresponding mRNA in response to environmental stimuli is clearly using the claimed invention as an object of scientific investigation in order to determine this information about the claimed nucleic acid molecules themselves.

Furthermore, the specification does not disclose any specific information about the expression pattern or level of the corresponding mRNA, nor does it describe how this missing information could be put to a specific use in obtaining a practical benefit. Consequently, one skilled in the art would first be required to determine the tissue distribution of the corresponding mRNA or to determine the level of expression of the mRNA in response to environmental stimuli. Then, one skilled in the art would have to develop a practical use for the information determined. Thus, the specification simply invites one skilled in the art to experiment on the claimed nucleic acid molecules with respect to detecting and measuring the corresponding mRNA in order to determine practical applications based upon the results obtained.

Footnote 9 of the brief (page 11) asserts that the claimed nucleic acid molecules can be used to determine the location of the corresponding genomic DNA sequences on a physical or genetic map without knowing anything more than SEQ ID NO: 1. The footnote merely summarizes what is stated at pages 11-12 of Appellants' response of 8/22/00 (which does not reference any articles) and in the Wiegand Declaration. This argument was addressed in the Advisory action of 11/22/00 at pages 12-14.

First, contrary to Applicants' assertion, it is not possible to determine the location of the corresponding genomic DNA sequences on a genetic map without knowing anything more than SEQ ID NO: 1. The placement of any locus on a genetic map requires that the locus be defined by two or more alleles which can be followed after meiosis (sexual reproduction) with respect to alleles of one or more other loci. Alleles of a locus can be distinguished from each other based on physical differences, e.g. sequence polymorphisms, in the genomic DNA (i.e. genotype), and/or based on phenotypic differences. The specification discloses no phenotypes associated with the claimed nucleic acid molecules nor does it disclose any physical differences in the corresponding genomic DNAs of various soybean isolates that can be detected with the claimed nucleic acid molecules. Appellant has repeatedly failed to explain how one skilled in the art can be expected to determine a genetic map location for the corresponding genomic DNA sequence knowing only SEQ ID NO: 1. Also, the Examiner never contended that one could not determine the corresponding location in a physical map experimentally, only that one could not determine the physical location knowing only SEQ ID NO: 1. However, the specification does not disclose a physical map location for genomic DNA corresponding to SEQ ID NO: 1, nor does it disclose how knowing the physical map location of the corresponding genomic DNA can be put to any practical purpose.

Second, using the claimed nucleic acid molecules to determine the location of the corresponding genomic DNA sequences on a physical map (or on a genetic map), constitutes investigation on the claimed invention to determine what chromosomal location can be detected

using the claimed nucleic acid molecules. Until the chromosomal location corresponding to the claimed nucleic acid molecules is known, one skilled in the art cannot use the claimed invention to study any other chromosomal locus, gene, or trait that may be linked to the corresponding chromosomal location. The specification fails to identify any chromosomal locus, gene, or trait that is linked to the chromosomal location corresponding to the claimed nucleic acid molecules, and thus fails to identify any chromosomal locus, gene, or trait for which the claimed nucleic acid molecules may be used in the capacity of a molecular marker, as asserted.

Simply because those skilled in the art have used other *characterized* molecular markers for defined traits or characteristics in genetic mapping (of linked loci), marker-assisted breeding, transgenic crop production, crop monitoring diagnostics, gene identification (presumably of other genes), etc., does not mean that the claimed nucleic acid molecules can necessarily be used for any or all of these purposes. Using the claimed nucleic acid molecules in the capacity of a probe for a molecular marker, e.g. a polymorphism, is simply a speculative use for the claimed nucleic acid molecules that would require experimentation in order to determine a specific and substantial use, if any, for the claimed nucleic acid molecule, such as being a molecular marker for some particular trait of interest, e.g. drought tolerance. *Response to Brief Section 8.C.(1)(a).*

Appellants argue that the claimed nucleic acid molecules have utility as a "tool" useful to "locate and measure nucleic molecules such as mRNA or chromosomal DNA that hybridize

to, but that do not consist of, consist essentially of or comprise SEQ ID No. 1 or its complement." The brief does not indicate any source for the hypothetical nucleic acid molecules described (brief, page 12), but based on the specification, it is presumed that these hypothetical nucleic acid molecules are to be found in other plant species. The argument in the brief compares the claimed invention to a microscope, a gas chromatograph, or an unspecified screening assay. This argument was first raised in the after-final response filed 8/22/00 at pages 8-9, and was responded to in the Advisory action at pages 8-9 (not 9-10).

A microscope is useful for determining structure of *any* sample of interest at the macroscopic, microscopic or molecular level, depending on the type of microscope. It is a generally useful tool for a wide range of specific uses. One does not usually use a microscope to study related microscopes. In contrast, Appellant argues that the claimed nucleic acid molecules are useful to detect or measure nucleic acid molecules that possess a certain level of structural relatedness to the claimed nucleic acid molecules, the level of relatedness being defined by hybridization to the claimed nucleic acid molecules. However, the only such nucleic acid molecule that is disclosed in the specification is one that "consist[s] of , consist[s] essentially of or comprise[s] SEQ ID No. 1 or its complement"; the specification discloses *no* nucleic acid molecule that hybridizes with the claimed nucleic acid molecules that does *not* "consist of , consist essentially of or comprise SEQ ID No. 1 or its complement". Therefore, it is unclear why Appellant takes issue with the statement in the Advisory action that "the

claimed nucleic acid molecule can only be used to identify a nucleic acid molecule complementary to itself" since that is the only nucleic acid molecule that the specification discloses that can be identified by hybridization. Furthermore, in order for hybridization between two nucleic acid molecules to occur, a part of each nucleic acid molecule **must share** at least some nucleotide sequence that is fully complementary. The length of fully complementary sequence required to detect hybridization depends primarily on the stringency of the specific hybridization conditions employed, the lower the stringency the shorter the length of fully complementary sequence required. The specification also fails to disclose any hybridization conditions required for detecting nucleic acid molecules that do *not* contain the nucleotide sequence of SEQ ID NO: 1 or its complement (other than subsequences of SEQ ID NO: 1 itself), in addition to failing to disclose any source for such nucleic acid molecules.

All arguments pertaining to the utility of the claimed invention with respect to studying the corresponding genomic DNA and mRNA found in soybean, would also apply to any homologous nucleic acid molecules found in other plant species. In so much as the specification fails to describe a specific and substantial utility for the corresponding nucleic acids in soybean, so does it fail to describe a specific and substantial utility for the corresponding nucleic acids in other plant species.

E) Response to Brief Section 8.C.(1)(b).

Appellants' arguments are directed to the use of the claimed nucleic acid molecules as probes to detect polymorphisms. It is asserted (brief page 13) that the final Office action

"provides no support (legal or factual) for the proposition that before detection of polymorphisms can be recognized as a legal utility, actual polymorphisms must be shown to exist". The specification (page 28, full para. 4) defines "polymorphism" as "a variation or difference in the sequence of the gene or its flanking regions that arises in some members of a species" (emphasis added). The specification from page 29 through page 35, line 3 discusses various types of sequence polymorphisms and how they are detected. The specification describes two general uses of sequence polymorphisms which can be detected with a nucleic acid molecule, such as the claimed nucleic acid molecule, used as a hybridization probe. First, a polymorphism serves as a molecular marker for a mutation that affects the expression of a product encoded, at least in part, by the nucleic acid molecule, i.e. the mRNA or protein corresponding to the nucleic acid molecule. The polymorphism can then be used to determine whether a particular phenotype is conferred by the mutation, e.g. by linkage analysis of the polymorphism relative to the phenotype. If the mutation is found to confer a phenotype, then the polymorphism serves as a molecular marker for both the phenotype and the mutation (specification, page 27, line 9 through page 28, line 6). Second, the polymorphism serves as a molecular marker for desirable traits that are genetically linked to the polymorphism, i.e. traits that are conferred by genes located on a chromosome very near the genomic location corresponding to the nucleic acid molecule (specification, page 35).

These uses for a nucleic acid molecule, which like the claimed nucleic acid molecule is an EST, are general in the sense that any EST has potential use as a probe to detect a

polymorphism, but only IF such a polymorphism exists. To determine whether a polymorphism exists at a specific chromosomal location requires hybridization to at least two individual chromosomes, and generally involves analyzing genomic DNA from multiple members of a species; the specification discloses no such analysis. The specification fails to disclose: 1) whether the claimed nucleic acid molecule can in fact detect a polymorphism, or even whether such a polymorphism exists; and 2) at least one specific example of at least one of the types of polymorphisms described in the specification (pages 29-35). There is also no evidence of record that polymorphisms detectable by the claimed nucleic acid molecule were known to exist prior to Appellant's filing date. The specification does not disclose any utility in this context for a nucleic acid molecule or EST that can not detect a polymorphism. Therefore, using the claimed invention to first determine whether or not the claimed nucleic acid molecule can, in fact, detect a polymorphism *is* to determine whether or not the claimed invention has a utility that requires detecting a polymorphism, i.e. it is "use testing" and not substantial. Since the specification fails to identify even one specific polymorphism that can be detected with the claimed nucleic acid molecule, the specification fails to show any specific correspondence between the disclosed general utility and the claimed subject matter, regardless of any specific application requiring detection of polymorphisms.

Furthermore, these uses for a nucleic acid molecule are general in the sense that any gene corresponding to an EST has the potential to confer a detectable phenotype if mutated or has the potential to be genetically linked to a desirable trait. Thus, any polymorphism that can

be detected with the nucleic acid molecule has the potential to serve as a marker for such a mutation or phenotype. However, the specification does not disclose that the gene corresponding to the claimed nucleic acid molecule is mutated in any soybean cultivars or that such a mutation confers any phenotype (useful or not) or that making such a mutation would confer any particular phenotype. The specification also fails to disclose any desirable trait that is closely linked to a polymorphism that could be detected with the claimed nucleic acid molecule. Since the specification fails to identify even one such mutation or desired phenotype that can be "marked" by a polymorphism detected with the claimed nucleic acid molecule, the specification fails to show any specific correspondence between the disclosed general utilities and the claimed subject matter. The process of identifying any hypothetical mutation in the corresponding gene and then identifying any phenotype conferred by the mutation, or the process of identifying any desired phenotype that could be "marked" by the polymorphism *is* solely a process of identifying a use for the claimed nucleic acid in this context, i.e. such use is not substantial.

The claimed invention is compared to a gas chromatograph (brief pages 13, 14). However, the logical basis for this analogy is unclear. Gas chromatographs are used to analyze any chemical compound, known or unknown, that can be put into the gaseous state. Those skilled in the art use gas chromatographs to analyze both known and unknown compounds. When the compound is unknown, the results obtained are compared to results for known compounds, e.g. standards. Appellants compare the failure to detect a polymorphism

with the claimed nucleic acid molecules, to the failure to detect a specific known compound in a sample, e.g. chlorine in an oil sample. This analogy fails address Appellants' own definition of the term "polymorphism". The specification (page 28, full para. 4) defines "polymorphism" as "a variation or difference in the sequence of the gene or its flanking regions that arises in some members of a species." It follows from this definition that if there is no "variation or difference in the sequence of the gene or its flanking regions" among "members of a species", then no polymorphism exists, i.e. a polymorphism is absent, in this region of the genome. A "polymorphism" is a collective concept defined by at least two variants (or alleles) found within members of a species collectively. Thus, one detects the *presence* of a polymorphism by analyzing multiple members of the species, i.e. analyzing a population. While one can detect the absence (or presence) of a specific allele of the polymorphism in a specific individual member of the species, one cannot detect the *absence* of a polymorphism *per se* based on one individual alone. The absence of a particular allele necessarily means that a different allele is present. The specification fails to disclose a specific and substantial utility for the claimed invention in the capacity of detecting polymorphisms, because it does not disclose whether the claimed nucleic acid molecules can, in fact, be used to detect any polymorphism whatsoever. Thus, the specification leaves open the possibility that there may be no polymorphism to detect. The specification fails to teach any polymorphism or any significance for a hypothetical polymorphism. Consequently then the activity for finding such polymorphisms is neither specific or substantial. With respect to the gas chromatograph

analogy, one can only detect the absence of a compound, such as chlorine, in a sample, *if* it was already known that chlorine could, in fact, be detected by the gas chromatograph were it present in the sample.

Appellants' argue that this use for the claimed invention is not use testing "because it determines information about the plant and its genetic traits, not additional information about the claimed nucleic acid sequence". However, the specification does not disclose any such "information about the plant and its genetic traits". Rather, the specification describes in very general terms the uses to which other, presumably prior art, nucleic acid molecules have been put in order to "determine information about the plant and its genetic traits." Consequently, it is left wholly for one skilled in the art to determine whether or not the claimed nucleic acid molecules can, in fact, be used to identify a polymorphism, which is use testing. Then, if a polymorphism can be detected, it is left wholly for one skilled in the art to determine if, in fact, the polymorphism can be used as a molecular marker for at least one phenotypic trait of interest, and if so, which one. This is also use testing.

At page 13 of the brief, Appellants assert that the credibility of this utility was challenged in final Office action at page 10. However, the final Office action did *not* challenge the credibility, i.e. operability, of identifying polymorphisms. In footnote 10 of the brief (page 13), Appellant argues that "the use of the claimed nucleic acid molecules to identify the presence or absence of polymorphisms is a use of the claimed nucleic acid molecules, not a preparatory step for another use". However this "use" is *not* a specific and

substantial use as required under 35 USC 101. As stated in the rejection *supra*, the specification does not disclose any utility in this context for a nucleic acid molecule or EST that does not detect a polymorphism. Therefore, using the claimed invention to first determine whether or not the claimed nucleic acid molecule can, in fact, detect a polymorphism *is* to determine whether or not the claimed invention has utility in a method that requires detecting a polymorphism. It is therefore a non-statutory use that is " a preparatory step for" a specific and substantial use, i.e. it is "use testing"; and the fact situation in *Kirk* clearly applies. If Appellants' argument were applied to the fact situation in *Kirk*, it would have been argued that using the claimed steroids to identify their biological activity would be "a use of the claimed" steroids, "not a preparatory step for another use", such as using the claimed steroids consonant with the biological activity identified.

With respect to comparing this utility to that of a "cell-based screening assay", Appellants assert that the Examiner implied that a diagnostic test such as ELISA has no utility because it does not identify useful ligands. However, Appellants' argument raised on pages 8-9 of the after-final response of 8/22/00 (answered in the Advisory action in the paragraphs bridging pages 8-9, rather than page 10) compared using the claimed invention to that of a cell-based assay "used to screen for desired compounds" such as ligands that bind to a receptor involved in a biological process. Such an assay is not comparable to an ELISA diagnostic assay (which is an antibody-based assay, not a cell-based assay) aimed at detecting a compound, such as detecting an antigen from a pathogenic bacterium in a blood sample. Page

11 of the Advisory action responds to a separate argument raised in the after-final response at page 10, where identifying polymorphisms using the claimed invention was compared to "a biological screen for chemicals which themselves might not have legal utility"; arguing that the assay itself and products used therein would still have utility. No more details concerning this hypothetical assay were mentioned, specifically no allusion was made to a diagnostic assay such as ELISA; nor was any legal basis provided on utility. It was this latter hypothetical assay that was compared to *Brenner*, since it had been assumed that the goal of the method was the "chemicals" identified, not the information provided by the assay, such as would be the case in a diagnostic assay. The Examiner stands by the rebuttal to Appellants' original argument regarding assays designed to identify "desired compounds" that themselves have no known utility.

Appellants (brief, top of page 15) compare "identifying the presence or absence of a polymorphism" for determining whether two organisms share a genetic heritage to an ELISA diagnostic assay. This analogy is similar to that of the gas chromatograph discussed above, and the same response applies to this analogy. The claimed invention cannot have any use in this capacity unless it was already known that there was a polymorphism to detect and that some specific and substantial activity was known for the polymorphism. However, the specification fails to disclose that there was, in fact, any polymorphism in the corresponding soybean genome, or any other genome, that could be detected with the claimed invention.

Finally, on page 15 of the brief, Appellant states that these issues "are beside the point because the claimed nucleic acid molecules did identify a polymorphism", referring to the results presented in the Wiegand Declaration (paras. 20, 23). However, these issues are not "beside the point" because the specification left the question open as to whether a polymorphism could, in fact, be detected and did not identify any polymorphism that could be detected. In *Kirk* at page 52, the Petrow declaration had shown that some of the claimed compounds actually had a specific biological activity, however, this finding was not deemed dispositive by the Court because it is "what the compounds are *disclosed* to do that is determinative". As with the Petrow declaration in *Kirk,* the Wiegand Declaration (paras. 20-23) is not dispositive here.

Furthermore with respect to the Wiegand Declaration, the specification does not define a "polymorphism" in the context of sequence variation between species, such as between *Glycine max* (soybean) and *Glycine soja* (wild soybean), nor does the specification teach any utility for detecting sequence variation between species of the genus *Glycine*. (In fact the specification does not even mention *Glycine soja* or any other species of *Glycine*.) The brief (page 15) asserts that it is not true that *G. max* and *G. soja* are different species because they can interbreed to produce fertile offspring, citing a definition obtained from "Oxford Dictionary of Biochemistry and Molecular Biology" (footnote 14). However, the cited reference has not been provided and cannot be evaluated in this context. In taxonomy, the capitalized first term is the genus name for an organism and the second term is the species

name for an organism. The fact that *G. max* and *G. soja* have been given different species names means that they are considered by those skilled in the art, particularly in *Glycine* taxonomy, to be separate species; not "soy varieties" as asserted in the brief. According to the National Center for Biotechnology Information, these two plants are currently considered to be separate species of the genus *Glycine* (see Taxonomy Browser on the World Wide Web at ncbi.nlm.nih.gov/htbin-post/Taxonomy). Furthermore, Ahmad et al. (J. Hered. 70: 358-364, 1979) discloses that "Chromosomal differentiation together with wide genetical and morphological differences provide evidence that *G. max* and *G. soja* are two distinctly separate species" (p. 363, col. 2), despite the fact that they can be interbred. Thus, those skilled in the plant taxonomy art, had considered and still consider these two plants to be separate species. Therefore, the example provided in the Wiegand Declaration of detecting sequence variation between species of a genus, *G. max* and *G. soja*, is not a utility disclosed in the specification. Polymorphism is defined in the specification in the context of members of a species, not species of a biological genus. Rather the Wiegand Declaration is an attempt to add subject matter to the specification for which there is no support in the original application.

In addition, the Wiegand Declaration (para. 22) states that "twenty restriction digests" of chromosomal DNA from *G. max* and *G. soja* were examined. (As noted above, the observed "polymorphism" between *G. max* and *G. soja* does not meet the definition for polymorphism set forth in the specification.) The "twenty restriction digests" are presumed to mean chromosomal DNA digested with each of twenty different restriction endonucleases.

"Polymorphism" could be detected in four of the twenty digests. The results shown in Exhibit C of the declaration presumably show the results for these four digests, and for one (*Hin*dIII) of the sixteen digests in which no evidence of "polymorphism" could be detected. This experiment is a good example of "use testing" - to determine with which, if any, of the twenty restriction digests the claimed nucleic acid molecules would detect a "polymorphism". The declaration shows that the claimed nucleic acid molecules have *no* use for detecting a polymorphism in 80% (16 of 20) of the digests. This information is not disclosed in the specification. Appellants' argument side-steps the issue. The determinative issue is what properties the instant specification discloses for the claimed nucleic acid molecules, not what properties were later discovered. As an analogy to the opinion of the Court in *Kirk* (at page 52), while the declaration may show that the claimed nucleic acid molecules do *in fact* detect a "polymorphism" between *G. max* and *G. soja* in four of twenty restriction digests, the original specification as filed did not contemplate any such properties.

F) Response to Brief Section 8.C.(1)(c).

The brief (page 16) asserts that the claimed nucleic acid molecules have use as probes for other molecules or as a source or primers. The specification (page 24) teaches that the claimed nucleic acid molecules can be used to isolate nucleic acid molecules from other plant species, such as nucleic acids that encode a homologue of the polypeptide corresponding to the claimed nucleic acid molecule. However, the specification fails to disclose any such nucleic acid molecules from other plant species. Nor does the specification teach what use these

nucleic acid molecules of other plant species would have. Any uncharacterized nucleic acid molecule from a species of organism can be used in this manner, thus such a utility is not specific to the claimed invention, and since the specification discloses no biological function or any use for any gene corresponding to the claimed nucleic acid molecule, any such nucleic acid molecules of other plant species would also lack substantial utility - the artisan would first have to experiment to determine a specific, substantial and credible use for any such nucleic acid molecules isolated.

The specification (pages 25-27) also teaches that the claimed nucleic acid molecule would have utility for initiating a chromosomal walk in order to isolate transcriptional regulatory sequences and promoters, including those of the gene corresponding to the claimed nucleic acid molecule. The specification (page 26, lines 6-8) teaches that the "ESTs isolated from the library of the present invention are used to isolate promoters of tissue-enhanced, tissue-specific, developmentally- or environmentally-regulated expression profiles". The specification draws on the prior art to teach how promoters may be identified. Significantly, the specification does not disclose any promoters at all, much less a promoter corresponding to the claimed nucleic acid molecule. Furthermore, the specification does not disclose whether expression of the corresponding gene, or any other gene within "chromosome walking" distance of the corresponding gene is tissue-enhanced, tissue-specific, developmentally- or environmentally-regulated. The fact that the corresponding gene is expressed in young seed pods does not indicate how the expression of the gene is regulated. Since the Wiegand

Declaration (para. 17) discloses that the corresponding gene is also expressed in young sprouts and adult leaf at roughly the same level. However, there is no evidence that expression of the corresponding gene is either tissue-enhanced or tissue-specific. Further, there is no evidence of record to indicate whether or not its expression is developmentally- or environmentally-regulated expression. In any case the original disclosure contains no such information.

Also, using a nucleic acid molecule, such as an EST, as a starting point for a chromosome walk in an effort to isolate a promoter is a general characteristic common to nucleic acid molecules isolated from any organism. This is a utility not specific to the claimed polynucleotide. Furthermore, since the specification does not disclose any specific promoter, either from the corresponding gene or from a gene linked to the corresponding gene, the specification lacks any specific correspondence between the claimed nucleic acid and any specific product, i.e. promoter, that could be made using it. The specification fails to provide for a specific utility for the claimed nucleic acid molecules in this capacity as an intermediate to obtain a theoretically useful product simply because it fails to disclose or describe any specific useful product that could be made. Rather, the specification merely directs one skilled in the art to use the claimed invention to go out and hunt for such a promoter, and after characterizing that promoter, determine what specifically to use it for. Thus, Appellants' argument is not persuasive.

While the specification teaches (page 24, para. 3) that the claimed nucleic acid molecules "*may be employed* to obtain other nucleic acid molecules" (emphasis added), the

specification does not indicate that any such nucleic acid molecules *had been* obtained, nor does it describe any characteristics possessed by such nucleic acid molecules. As to whether such molecules could, in fact, be obtained, the Office can neither prove nor disprove the assertion because the Office does not have laboratory facilities. At the time the application had been filed, future experimentation on the part of one skilled in the art would have been required to determine which, if any, other plant species contained nucleic acid molecules that could have been obtained using the claimed invention, and under what experimental conditions.

With respect to using the claimed nucleic acid molecules to initiate a chromosome walk, such as to isolate a promoter of the corresponding gene, this issue is discussed at pages 12-13 of the final Office action and pages 15-16 of the Advisory action rather than the pages indicated in the brief. The final Office action did not "denigrate" this potential utility, it merely explained why the specification failed to support it with the degree of particularity required to confer *immediate* benefit to the public. Specifically, the specification fails to disclose any characteristics of the corresponding promoter, or any other promoter within "chromosome walking" distance; neither structural characteristics, by which the promoter might be identified, nor functional characteristics, by which a specific and substantial use for the promoter might be determined.

In this context, the claimed invention does not compare to a golf club, because one knows what a golf ball is and how to use the golf club to hit it, whereas the specification does

not disclose or describe with particularity any known useful nucleic acid molecule that can be obtained, such as the corresponding promoter - it simply invites the skilled artisan to provide such information by further experimentation.

Even assuming, *arguendo,* that the corresponding promoter exists there is no more guidance for its isolation, and eventual use, than knowing that a haystack contains a needle - at least one is presumed to know what the needle looks like. Also, the specification does not disclose the distance or direction one has to walk on a chromosome from the corresponding location to reach the corresponding promoter. Thus, starting the walk at the corresponding chromosomal location is no more help in identifying the promoter than is picking a specific location in a haystack to start looking for a needle when one does not know where the needle is relative to the starting location. Initiation of a chromosome walk at the corresponding chromosomal location is considered non-specific because any EST would serve the purpose for isolating an uncharacterized promoter, since any chromosomal location is expected to be linked to a promoter. The Examiner agrees that not just any EST would serve in isolating the promoter corresponding to the claimed nucleic acid molecules, but since the specification asserts only that the promoter exists, this agreement is moot. As to whether one skilled in the art may be able to eventually identify and isolate the corresponding promoter, using the teachings of Birren et al. for example (no copy has been provided by Appellant), this is irrelevant, particularly since the corresponding promoter was and is unknown (and presumably not described in Birren et al.). The specification fails to disclose sufficient characteristics of

the corresponding promoter, such as its sequence or precise location relative to the genomic location corresponding to the claimed nucleic acid molecule, to inform one of what the corresponding promoter is or when it has been isolated. For example, a nucleotide sequence is identified during the chromosome walk as a putative promoter by sequence analysis, is then subcloned into operable linkage with a reporter gene and transfected in into young soybean seed pods cells, but found not to express the reporter gene in the cells. This result could mean the putative promoter: is not truly a promoter, i.e., a false positive; is not the corresponding promoter; or is incomplete, i.e., lacked additional sequence elements required for promoter activity in the seed pod cells. As indicated in the brief (bottom of page 18), substantial utility means that "one skilled in the art can use a claimed discovery in a manner which provides some *immediate* benefit to the public", *Nelson v. Bowler*, 206 USPQ2d 881, 883 (CCPA 1980) (emphasis added). Since the specification does not describe the corresponding promoter, or any other specific nucleic acid molecule, sufficient to inform one skilled in the art that it has been isolated, there can be no "*immediate* benefit to the public" in using the claimed nucleic acid molecule in this capacity; "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion", *Brenner* at page 696.

G) Response to Brief Section 8.C.(2).

The issue here is whether the general disclosure of potential uses for the claimed nucleic acid molecules, without disclosure of the specific details of such use corresponding to the claimed nucleic acid molecules themselves, meets the requirement for a substantial utility,

i.e. is there some immediate benefit provided to the public. Appellant argues that the Wiegand Declaration provides proof that the claimed invention is operable for at least two utilities, e.g. "to detect the presence or absence of a polymorphism". In *Kirk*, the court was not persuaded by *ex post facto* evidence that the claimed invention was useful under §101 because the specifics of that use were not disclosed in the specification. As in *Kirk* (page 53), the Wiegand Declaration here is an attempt "to add statements of usefulness to the disclosure of the application as filed", and as such is "irrelevant to the issue of adequacy of the original disclosure". For example, the original specification does not even mention a use for the claimed invention in detecting sequence variation between *G. max* and *G. soja*, for breeding or any other purpose, nor does it describe the nature of the sequence variation to detect. That Wiegand Declaration was required to introduce such a use, and to supply the details for carrying out that use, shows that the claimed invention could not have provided "some *immediate* benefit provided to the public." First, research on the claimed invention itself was required, to determine whether it did have such a use, and, if so, how to use it, e.g. hybridize to an *Eco*RI chromosomal digest rather than to a *Hin*dIII digest, or any one of the fifteen other enzymes that were not found useful, Wiegand Declaration para. 22 and Exhibit C.

This situation is not analogous to that in *Nelson* where the original *specification* (not an *ex post facto* affidavit) disclosed very specific pharmacological activities for the claimed compounds that the court deemed an adequate showing of practical utility. The court specifically contrasted the situation with that in *Rey-Bellet v. Englehardt*, 181 USPQ 453,

(CCPA 1974) where the disclosed evidence for pharmacological activity was deemed inconclusive, and thus failed to prove practical utility. In both cases, the claimed compounds were structural analogs for prior art pharmacologic compounds with known specific uses. The utility issue turned on whether evidence disclosed in the specification was sufficient to establish pharmacological similarity as well. That is not the case here: the original specification does not disclose any specific use for the claimed nucleic acid molecules other than using them to identify one, much less a known structural analog with a known specific use to which the claimed nucleic acid molecules can be compared.

With respect to the "real world" value of ESTs in general (brief, page 19), it is asserted that there is "no question that the public has recognized the benefits provided by the claimed subject matter, and has attributed "real world" values to such nucleic acid molecules". It is unclear as to what evidence Appellants are alluding. The evidence supplied by Appellants shows that a multimillion dollar industry has arisen surrounding buying and selling EST databases and clones, not that anyone in this industry has bought or sold the claimed subject matter. More importantly, however, footnote 18 acknowledges that simply because a product, such as an EST sequence database or clone library, is bought and sold does not mean it has patentable utility. The footnote goes on to state that buying and selling ESTs is evidence that ESTs are "related to the world of commerce". However, that a product is "related to the world of commerce," because it is bought or sold, does not mean that the product has patentable utility. Evidence that ESTs are bought and sold, or that ESTs are "related to the

world of commerce" because they are bought and sold does not identify a specific and substantial patentable utility. The evidence provided by Appellants in this regard does not establish any nexus between the commercial value of ESTs, in general, and specific and substantial utility under §101 of uncharacterized ESTs in general or the claimed subject matter in particular.

Appellant compares processes using ESTs to "industrial product[s] used in an industrial process" such as fermentation. This analogy is not persuasive. At least in fermentation, one has an idea of what one is making, e.g. beer or a specific recombinant protein. The specification does not describe any specific and substantial use for the claimed nucleic acid molecules in the capacity of making some other useful compound, because it describes no specific compound and no specific and substantial use for the compound made, e.g. the corresponding protein or mRNA.

H) Response to Brief Sections 8.C.(3), 8.C.(3)(a) and 8.C(3)(b).

The Examiner's points to which the brief alludes were raised in rebuttal to Appellants assertion in the response of 7/6/99 (page 6), where it was asserted that an EST, such as the claimed nucleic acid molecules, must correspond to an mRNA that is functional *in vivo*, and therefore has immediate use as a tool in commercial and experimental activity. In response to this argument, evidence and scientific reasons for doubting this oversimplified assertion were presented in the final Office action. Appellants conclude (brief, bottom of page 22) that unless the invention is proved "wholly inoperative," "the rejection must be withdrawn." However,

in order to meet the requirements of 35 USC 101, the specification must disclose at least one utility that is specific and substantial, as well as credible (absent a showing of well established utility, which would presume that the utility was credible). The claims have been rejected because 1) the specification fails to disclose at least one utility that is both specific and substantial, and 2) no convincing evidence has been presented to show that an EST, for which only its nucleotide sequence and source have been disclosed, has a well established utility.

The brief does not appear to directly argue for a well established utility for the claimed invention; however, the arguments concerning the commercial value of ESTs in general (brief, pages 19-21) may implicitly be directed to a well established utility for any EST in general, and the claimed nucleic acid molecules in particular. However, such evidence is not relevant to 35 USC 101.

I) Response to Brief Sections 8.D.(2), 8.D.(2)(a), 8.D.(2)(b).

Subsection (1) reprises the inseparable connection between patentable utility and the "how to use" requirement under 35 USC 112, first paragraph. Subsection (2) appears to question the propriety of rejecting claims 1 and 3 for not being commensurate in scope with the disclosure in terms of both how to make and how to use the invention. The Examiner maintains that the use asserted for the claimed invention are methods where the claimed invention is, itself, an object of scientific study, e.g. to determine the tissue distribution of corresponding mRNA embraced by the claims or to determine whether the corresponding

genomic DNA of soybeans contains a polymorphism that can be detected with the claimed invention.

Appellants argue that the rejection is improper on its face because the rejection only refers to uses that involve hybridization, either as a probe or as a primer. This concern is not well taken, because all of the other speculative utilities disclosed in the specification employ hybridization at some point using claimed nucleic acid molecules. In order for a primer to work in an amplification reaction, such as PCR, it must hybridize at least transiently with its intended target sequence. Appellant misapprehends the reason for the additional grounds of rejection under 35 USC 112, first para. which was directed to reasons for lack of enablement in addition to that dictated by the failure of the specification to disclose a specific and substantial utility. Regardless of whether the specification teaches a specific and substantial utility for using the claimed nucleic acid molecules as a probe for hybridization or as a primer in PCR amplification, the specification does not enable the full breadth of the claims for using the claimed invention in these manners, even if such use is only in the context of further scientific investigation of the claimed invention.

Footnote 29 suggests several utilities which were not addressed. Contrary to Appellants assertion, the detection of polymorphisms does involve hybridization between either probes or primers with a target nucleic acid (see specification, pages 28-35). With respect to antisense molecules, the issue of how to make and use them is inseparable from the reasons this use has no disclosed patentable utility. In any event, antisense molecules do act by

hybridizing to their target mRNA. With respect to transforming cells with the claimed nucleic acids or to raising antibodies, these utilities are directed to making and using, respectively, protein corresponding to the claimed nucleic acid molecules, *not* to the claimed nucleic acid molecules themselves. However, these utilities do require using the claimed nucleic acid molecules as hybridization probes, i.e. as an intermediate, in order to first isolate any corresponding nucleic acids that encode a corresponding protein (specification, page 12, para. 3). The specification does not teach any protein, nor any patentable utility for the protein, either as an end product or as an intermediate. The omission of these utilities from the enablement rejection is of no moment because the brief (at page 9, 2nd full para.) states:

> It is irrelevant whether the corresponding mRNA or polypeptide themselves have utility because Applicants are not relying on utility of the mRNA or polypeptide to establish utility of the claimed nucleic acid molecules.

However, the claimed nucleic acid molecules do embrace any corresponding mRNAs, and any complete cDNA copies thereof, since the disclosed EST is presumed to be a subsequence contained in these nucleic acids, and may embrace the corresponding genes or chromosomal DNA. The specification does not disclose whether SEQ ID NO: 1 is present in the corresponding gene or chromosomal DNA. For example, if SEQ ID NO: 1 contains a poly(A) sequence added during transcription, or is interrupted by an intron in the chromosomal DNA, then claims 1 and 3 would not embrace the corresponding gene or chromosomal DNA.

To summarize the additional grounds of rejection, the scope of claims 1 and 3 is astronomically huge, when one only considers additional nucleic acid sequences added to SEQ

ID NO: 1. While the claims do embrace nucleic acid molecules with predictable hybridization performance characteristics under certain well-controlled conditions, whether as a probe or a primer, the claims are not limited to such nucleic acid molecules, nor do the claims include any functional limitations or intended use limitations restricting their utility to one involving hybridization, or any other function. As pointed out by Appellant, the specification does disclose intended uses (not deemed to meet the utility requirement) that do not involve hybridization, e.g. production of the corresponding protein. The claims embrace many embodiments that would simply not function appropriately in hybridization (no hybridization or hybridization to non-target nucleic acid molecules), and the specification does not teach how to use the large number of embodiments that are inoperative for hybridization. This is not simply a situation where the claims embrace few inoperative embodiments (relative to the scope of the claim) in one disclosed use, e.g. hybridization.

For example, the Wiegand Declaration (at para. 13) states that one skilled in the art would know that addition of soybean sequences to SEQ ID NO: 1 would prevent efficient use of such a combined sequence as a hybridization probe for soybean nucleic acid molecules. However, this presupposes that one would know *a priori* whether any arbitrarily chosen nucleic acid sequence was or was not soybean nucleic acid or would or would not cross-hybridize with other soybean nucleic acid molecules. Such nucleic acid molecules are embraced by the claims.

The Examiner agrees with Appellants that the claims may include inoperative embodiments; however, only if the operative embodiments can be identified without resort to undue experimentation, and the claimed subject matter bears a reasonable correspondence with the enabled embodiments. See e.g. *In re Vaeck*, 20 USPQ2d 1438, 1444-1445, where the affirmance of the rejection of the broad claims was largely due to unpredictability. In *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 224 USPQ 409, 414 (CA FC 1984), the court qualified the statement:

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of the claims to specifically exclude * * * possible inoperative substances * * * *"

with the statement:

> Of course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid.

It is the latter situation at issue here.

The Examiner agrees with Appellant that lack of absolute predictability does not preclude enablement or that the requirement for " some experimentation ... does not preclude enablement", but holds that the wholesale "make-and test" experimentation required here to enable the full scope of the claims was not what the courts had in mind. In *Atlas Powder*, the specification in question contained ample guidance for the substituents in the claimed combinations. In contrast, the instant specification contains little guidance on the nature of additional sequences that might be attached to the sequence of SEQ ID NO: 1 for use in

hybridization or any other methodology. It is acknowledged that those of skill in the art were aware of various nucleic acids that could be conventionally attached to a probe without adversely affecting its performance characteristics in hybridization, such as a vector backbone or oligonucleotides such as linkers, adapters, or PCR heels (see Wiegand Declaration at para. 13). However, the claims are not limited to nucleic acid molecules further comprising such nucleic acids. The claims embrace adding to SEQ ID NO: 1 any additional nucleic acid, of any length or sequence, regardless of purpose. Adding nucleic acids of arbitrary length and sequence to a probe sequence, such as SEQ ID NO: 1, is *not* conventional in the art. There must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed, see *Vaeck* at page 1445. The specification does not teach which unconventional additional sequences would be consonant with using the claimed nucleic acid molecules in hybridization, nor does it teach how to use those claimed nucleic acid molecules that are unsuitable for hybridization.

The relevance of the "benzpyran" example (brief, page 30), which appears to be hypothetical, to the instant case is unclear. Nucleic acid molecules are not analogous to many types of product, such as benzpyrans. Those in the art employ nucleic acid molecules for many different uses, and these molecules are in heteropolymeric chains of a wide variety of different residue sequences and sizes, from oligonucleotides a few residues in length up to

chromosomes of 1,000,000 or more residues in length. Not all of these are suitable for uses requiring hybridization, nor would those skilled in the art even consider doing so.

Although the level of skill in the hybridization art is high and that the prior art provides ample general guidance on hybridization, the art also recognizes that choosing specific probes for a specific application must be taken on a case by case basis. The only explicit guidance in the specification with regard to a probe is SEQ ID NO: 1 itself. The only generally disclosed target nucleic acids disclosed are SEQ ID NO: 1 and the corresponding mRNA and genomic DNA from soybean and perhaps from other plants. Given this limited disclosure, it is unclear how one skilled in the art would use the vast majority of nucleic acid molecules embraced by the claims, which includes a nucleic acid molecule comprising SEQ ID NO: 1, 469 nucleotides long, attached to 1,000,000 nucleotides, or greatly more, of arbitrary sequence.

Appellants urge (brief, page 31) the concerns that the claims embrace inoperative embodiments "are irrelevant", citing *Atlas Powders* and *Ex parte Cole*, 223 USPQ 94, 95 (BPAI 1983) as support. However, *Atlas Powders* stated that if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. *Cole* is inapposite because the instant rejection is not based upon any argument that each embodiment be useful for each and every use. Only one use, hybridization, is at issue since the specification does not disclose any other use that does not require hybridization at some point. Furthermore, the claims in *Cole* each contained functional limitations or intended

use limitations in addition to structural limitations. The instant claims have no functional or intended use limitations.

Pages 31-36 of the brief summarize pertinent case law with respect to enablement and prior art references which show the state of the prior art and the skill of one in the pertinent art. Since the only working example shows using a claimed nucleic acid molecule, a *conventional* plasmid clone, as a template for PCR amplification, the second and third *Wands* factors do not appear to be met in this case. What is missing from the specification, and the general knowledge in the art, is guidance on the nature of additional nucleic acid added to SEQ ID NO: 1 for uses requiring hybridization.

While it is true that a considerable amount of experimentation is permissible if it is routine, i.e. typically performed by those in the pertinent art, that is not the situation here. The issue is not whether it is routine to try different hybridization protocols in order to optimize (see Wiegand Declaration, para. 11). The question is whether it is routine in the art to add arbitrary nucleic acid, of any length or sequence, to a defined probe sequence, e.g. nucleic acid molecule consisting of SEQ ID NO: 1, and whether it is routine to then test such complex probes for operability. The sheer magnitude of the embodiments claimed, i.e. infinite, is evidence that such an undertaking would be extremely laborious and lengthy. The problem here is that the claims embrace far more than would be conventionally employed for uses requiring hybridization. The Court in *Atlas Powders* stated that "if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the

art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid". That is the situation here.

J) Response to Brief Sections 8.E., 8.E.(1), and 8.E.(2).

The issue is whether Appellants was in possession of the genus being claimed (claims 1 and 3). This genus is not restricted to any particular disclosed subgenus or species, such as vectors comprising SEQ ID NO: 1 as an insert. The only nucleic acid molecules described by complete structure are the one consisting of SEQ ID NO: 1. The only nucleic acid molecules comprising or consisting essentially of SEQ ID NO: 1 described in the specification by other characteristics are generic vectors comprising SEQ ID NO: 1. While it is acknowledged that Appellant need not describe "every nuance" of the claimed invention, the written description must bear a reasonable correlation to that which is claimed. The disclosed subgenus and species embraced by the claims are not representative of the entire genus being claimed. The genus of nucleic acid molecules being claimed embraces any and every type of nucleic acid molecule that comprises SEQ ID NO: 1 and additional sequences of any size and sequence, not just vector backbones. Clearly, at the time of filing, Appellant was not in possession of genomic materials that contain the common EST fragment, which are embraced by the open-ended claims. The specification does not disclose what characteristics these additional sequences may or may not have that are consistent with the operability of the nucleic acid molecules as probes or primers for detection of SEQ ID NO: 1 in a target sequence, and all

disclosed uses for the claimed nucleic acid molecules are fundamentally as probes or primers, at least in some aspect.

With respect to full length mRNAs, cDNAs and genomic sequences, one skilled in the art would reasonably conclude that the claims embrace these nucleic acid molecules, and the specification provides no physical (i.e. structural) characteristics of these molecules to distinguish them from other nucleic acid molecules comprising SEQ ID NO: 1 and no other indication that would suggest Appellant possessed them. This particular subgenus embraced by the claims has a disclosed potential utility not possessed by those members of the claimed genus useful only in hybridization. Full length mRNAs, cDNAs and genomic sequences (genes) would encode the corresponding protein(s).

With respect to recitation in claim 3 of "consisting essentially of", the statement made in the Office action of March 22, 2000 at page 22, lines 10-14 was not intended to be a basis of the rejection. The statement was made to indicate why claims 1 and 3 were being treated the same in the rejection, i.e. that the specification provided no material limitation that would distinguish the subject matter of claims 1 and 3 from each other (see comment above). Appellant's statement indicates that claim 3 should exclude "ingredients that may materially affect" the use of the nucleic acid molecule as a probe. However, the specification does not describe what such ingredients might be. Also, this statement implies that claim 1 would include nucleic acid molecules that do comprise "ingredients that may materially affect" the use of the nucleic acid molecule as a probe or primer. The specification discloses no other use

for the claimed nucleic acid molecules. Consequently, if there is subject matter embraced by claim 1 that is excluded by claim 3, there is no indication in the specification that Appellant was in possession of such subject matter and therefore of the broader genus of claim 1. (See *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (CA FC 1997) where disclosure of a rat insulin cDNA did not provide support for claims to mammalian insulin cDNA or human insulin cDNA.)

A fundamental issue here is specific to the very narrow class of product that is nucleic acid molecules. The basic question upon which Appellants and the Examiner disagree is whether the disclosure of a partial sequence of otherwise uncharacterized nucleic acid molecules that may encode a corresponding protein is sufficient to establish possession of a broad genus based solely on the description of the partial sequence, where the broad genus embraces the uncharacterized nucleic acid molecules by default. The subgenus of uncharacterized nucleic acid molecules that encode any corresponding protein is explicitly alluded to in the specification, and disclosed as possessing an additional use *not* possessed by any other members of the broad genus being claimed, i.e. encoding the protein. The specification fails to provide any structural or functional characteristic for these desired nucleic acid molecules, which encode the protein, that would distinguish them from the other members of the genus, which simply comprise SEQ ID NO: 1 as the sole distinguishing feature. As stated in *University of California v. Eli Lilly and Co.* at page 1404:

> An adequate written description of a DNA ... "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

That Appellants claims embrace nucleic acid molecules that encode a corresponding protein, whatever it may be, is clearly evident from the specification and the brief (page 40). The Court in *University of California v. Eli Lilly and Co.,* at page 1405, further noted regarding generic claims:

> A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials. *Fiers*, 984 F.2d at 1171, 25 USPQ2d at 1606; *In re Smythe* , 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . .").

In the instant case, the only species specifically enumerated are the nucleic acid molecule of SEQ ID NO: 1 itself and the specific deposited clone on which it was isolated. The specific embodiments that in addition to SEQ ID NO: 1, include nucleic acids that will allow the corresponding protein to be encoded cannot be predicted without the coding sequence itself. This coding sequence has not been disclosed. Clearly, the specification would not show one skilled in the art that the these desired subcombinations were possessed by Appellant, and thus the embracing genus was also not possessed.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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